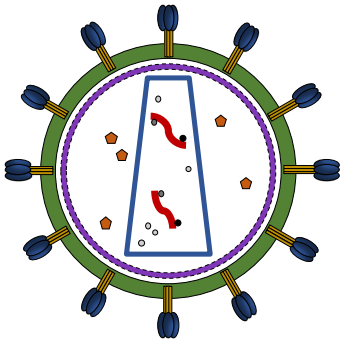
Engineered Immune-Mobilising Monoclonal T Cell Receptors for HIV Cure



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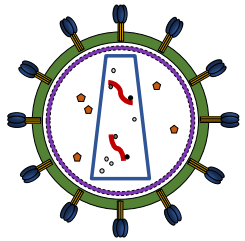
23rd Annual Conference of the British HIV Association

The HIV Reservoir



- HIV reservoir established early in HIV infection = barrier to a cure
  - Infection, integration → cells transition to a resting state
  - Long half life[1]: 73 years to eradicate 10^6 cells
- How to eliminate the HIV reservoir?
  - Early ART during PHI: lowers T cell activation & reservoir size[2,3]
  - 'Kick and Kill': latency reversal agents + immunotherapeutic

[1]Murray, A. et al., J. Imm. 2016 [2]Ananworanich, J. et al., EBio Medicine 2016 [3]Jain, V. et al., J Infect. Dis. 2013

Immune

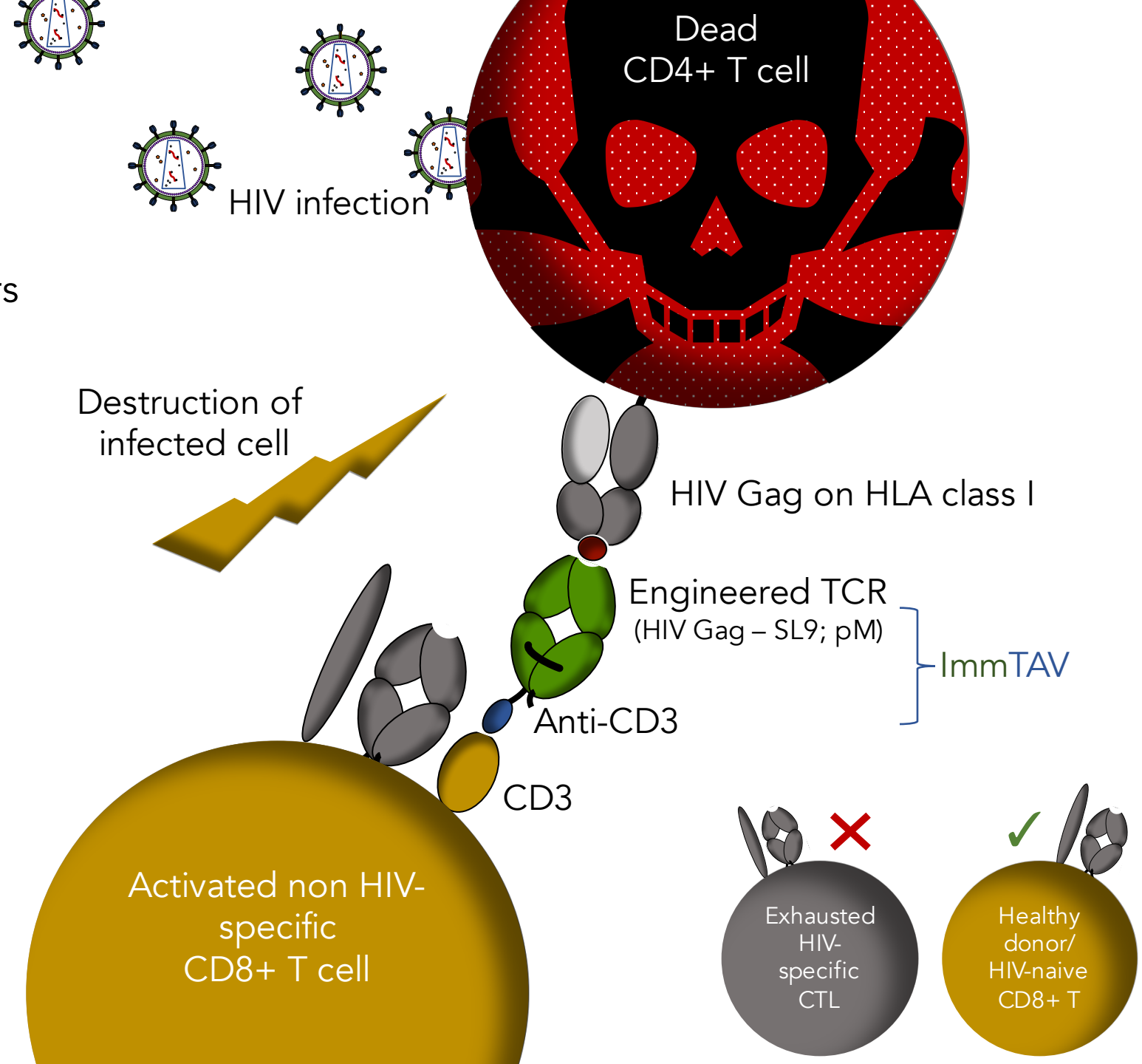
Mobilising

Monoclonal

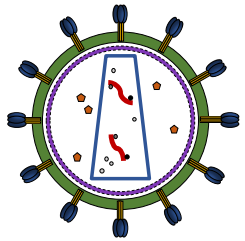
T cell receptors

Against

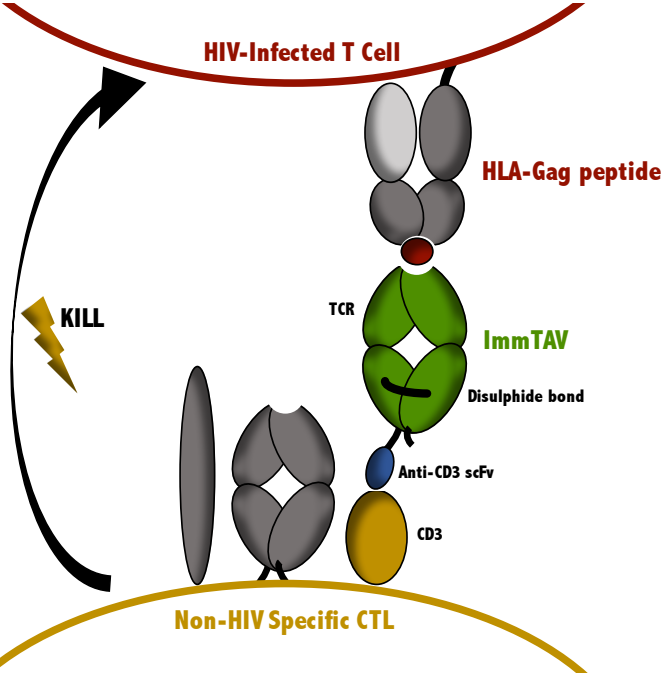
Viruses

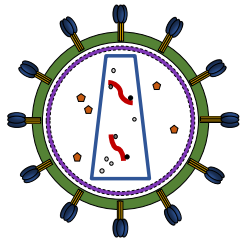


Aims



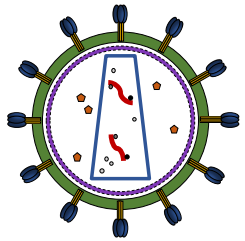
- Assess potency of HIV ImmTAV for redirecting CD8+ T cells from patients treated during PHI (SPARTAC cohort)
- Investigate susceptibility of HIV reservoir cells to ImmTAV-mediated killing using an in vitro latency model



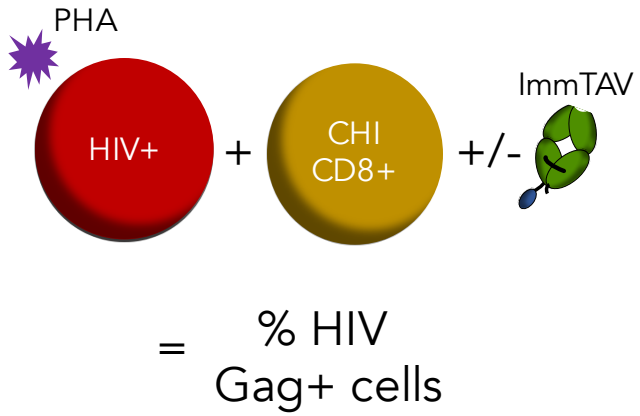


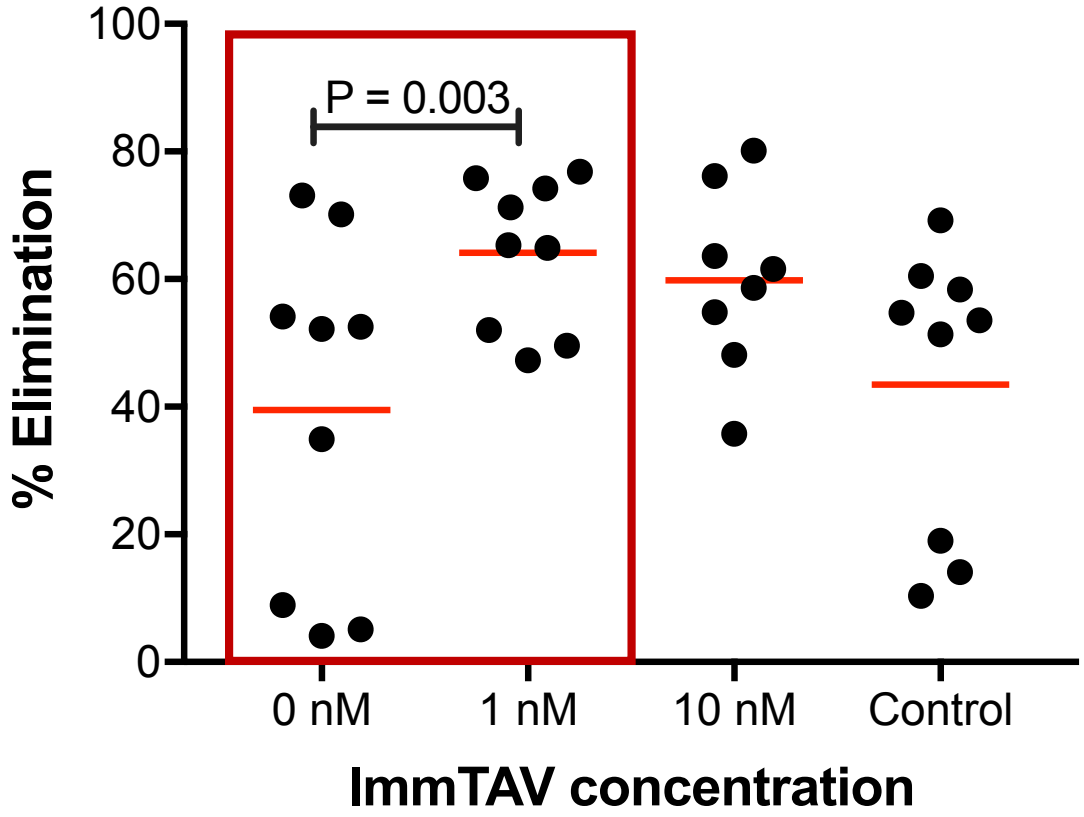
ImmTAV redirection of CD8+ T cells from patients treated during PHI

Antiviral efficacy of CD8+ T from PHI patients

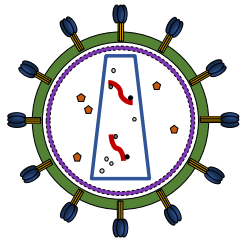


- SPARTAC: treated within 6 mo. of seroconversion
- Viral inhibition assay: flow cytometry



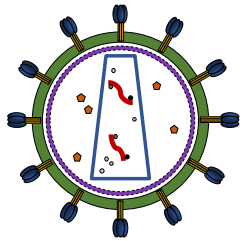


Conclusions



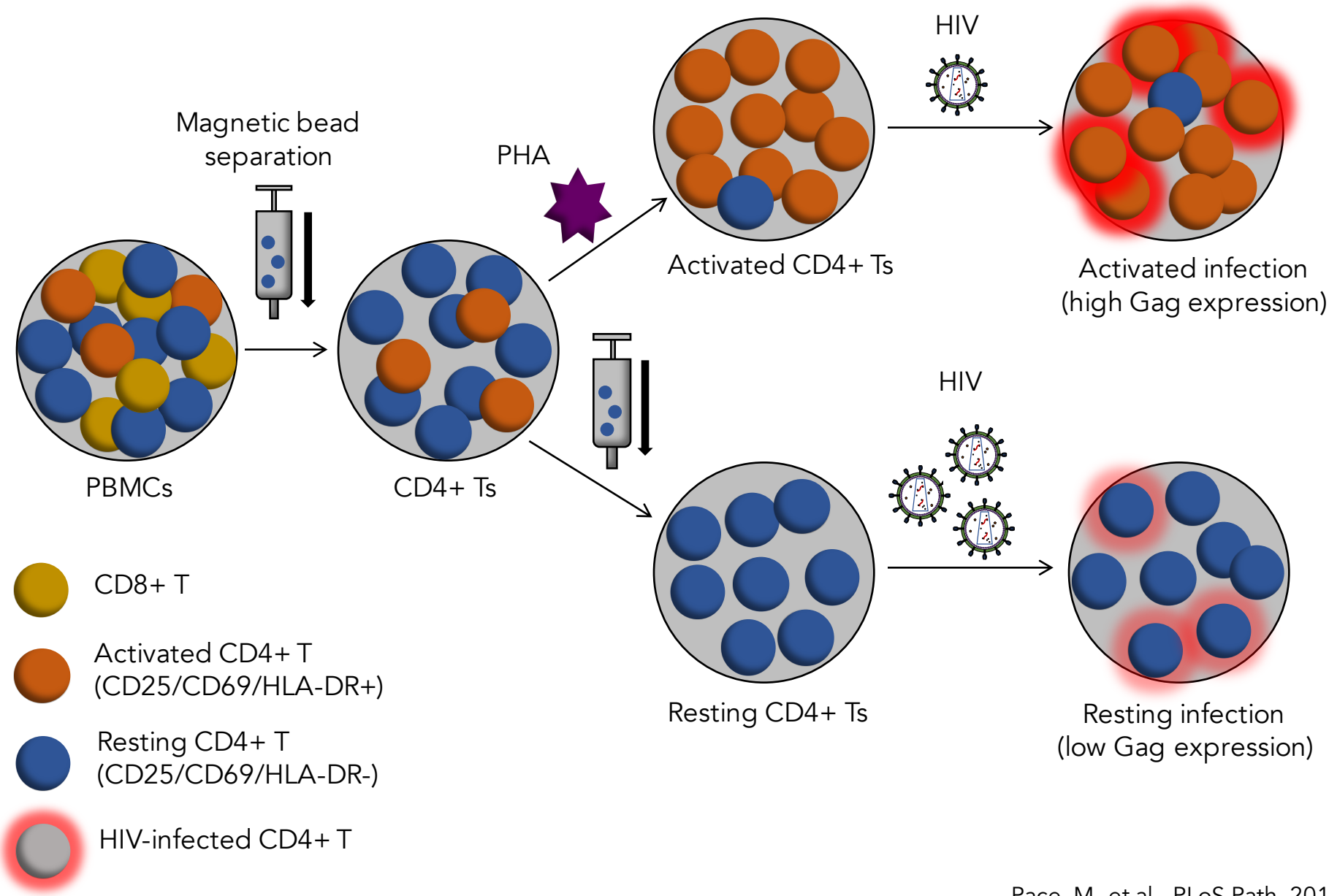
- ImmTAV redirection improved clearance of HIV+ cells
- Earlier treatment may be required for improved immunologic recovery
  - Comparable effect to chronic HIV patient CD8+ T[1]
  - Impaired antiviral activity compared to healthy donor CD8+ T even with ImmTAV redirection
- Further work to investigate impaired antiviral activity of CD8+ T cells from chronic patients (global)

[1]Yang, H. et al., Mol. Therapy 2015



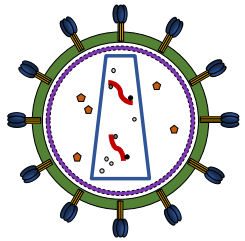
Susceptibility of HIV reservoir cells to ImmTAV-mediated killing

Latency model: resting cell infection

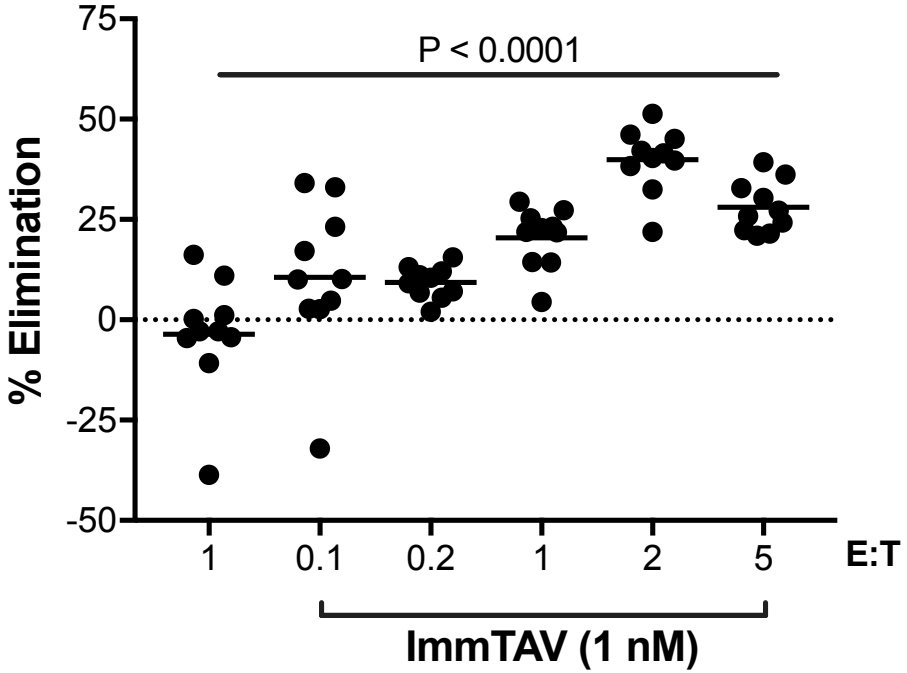


Pace, M. et al., PLoS Path. 2012

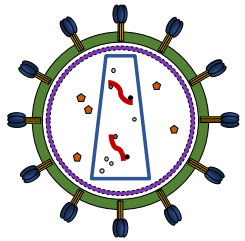
ImmTAV-redirected clearance of Gag+ reservoir cells



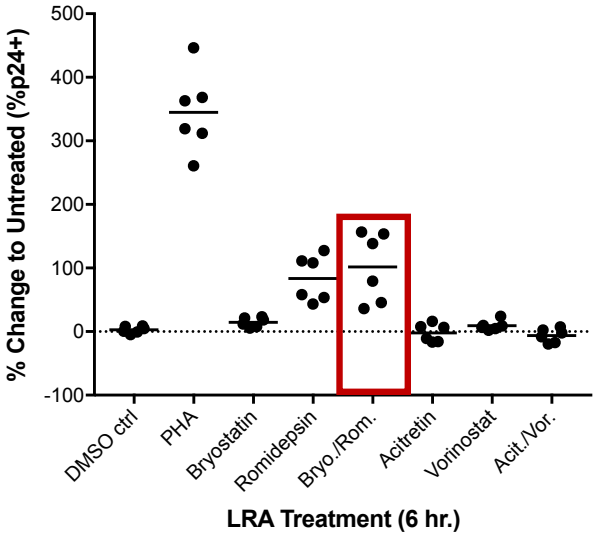
- Latency viral inhibition assay:
  - Resting, infected CD4+ T
  - Healthy donor CD8+ (E:T)
  - +/- HIV ImmTAV (m121)
- ImmTAV-redirected clearance of resting, infected T cells
  - Enough Gag visible for detection by ImmTAV without latency reversal
  - Maximum effect at 2:1 E:T

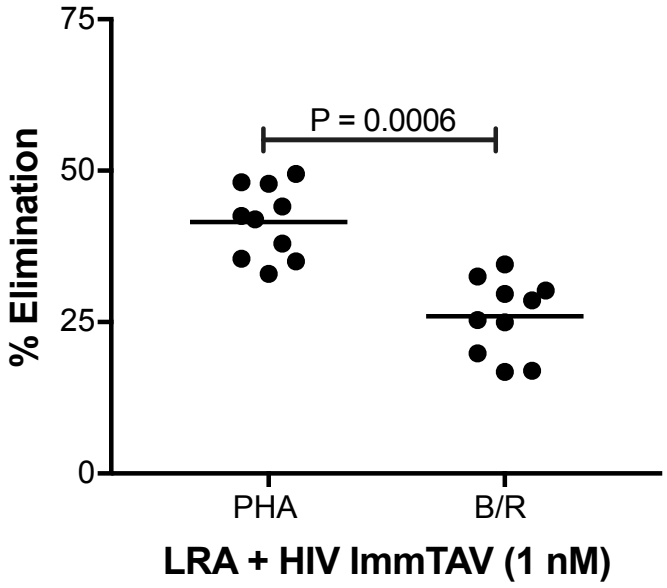


‘Kick and kill’: latency reversal agents + ImmTAV

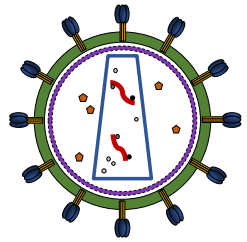


- Addition of LRA to reactivate latent HIV + redirection by ImmTAV
- Bryostatin/romidepsin provided best reactivation
- LRA + latency viral inhibition assay:
  - Increase Gag expression
  - Little effect on ImmTAV-mediated killing

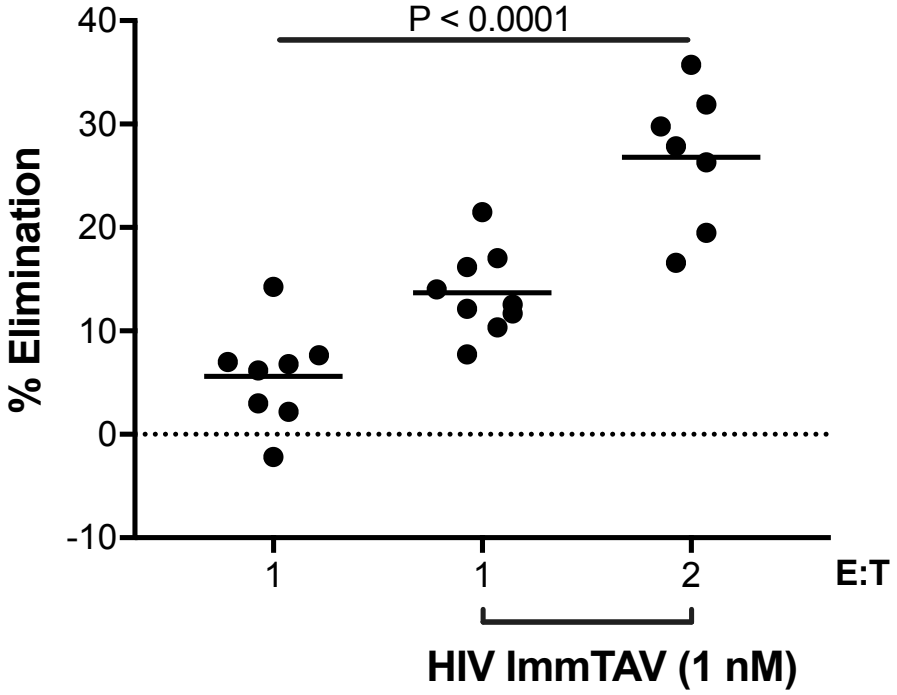




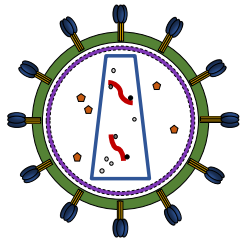
Impact of ImmTAV-redirection with chronic patient CD8+ T cells



- Latency viral inhibition assay:
  - Healthy donor resting, infected CD4+ T
  - CHI donor CD8+ T (E:T)
  - +/- HIV ImmTAV
- ImmTAV-redirection improves clearance of Gag+ reservoir cells by CHI CD8+ T
  - Low natural CTL response
  - Less than that seen with healthy donors

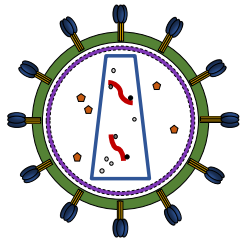


Conclusions



- HIV ImmTAV:
  - Significantly increases ex vivo elimination of HIV+ cells by CD8+ T cells from patients who began ART during PHI
  - Confers HIV-specific killing capacity on CD8+ T cells from healthy donors in a latency model
  - Enhances killing capacity of CD8+ T cells from CHI patients
- Implications:
  - HIV Gag expression in latent reservoir is heterogeneous: a subset may be susceptible to elimination by ImmTAVs without LRAs
  - HIV ImmTAVs have potential as component of eradication strategies (> natural TCR)

Thank you to…



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Thank you for listening – questions?

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IMMUNOCORE targeting T cell receptors

British HIV Association BHIVA

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